REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Summary of the Claims

Claims 23-34 and 44 are requested to be cancelled.

Claims 35-43 are withdrawn.

New Claims 45-52 have been added which correspond to previously filed claims 23-34.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. As the amendments to the claims do not introduce new matter, entry thereof by the Examiner is respectfully requested.

After amending the claims as set forth above, claims 45-52 are now pending in this application.

II. Objections to the Claims

The Examiner objected to claims 24-29 for the recitation of the phrase "wherein said protein" in referencing Smac and not TAT. Office Action at 3. Applicants have canceled claims 24-29 and added new claims 45-52 which specifically refer to the "Smac protein." Thus, Applicants believe this objection to be moot.

The Examiner also objected to claims 25-29 for allegedly being of improper form for failing to further limit the subject matter of a previous claim. Office Action at 3-4. Applicants have canceled claims 25-29 and added new claims 45-52 which Applicants believe to be of proper dependent form. Thus, Applicants believe this objection to be moot.

The Examiner objected to claim 27 for failing to recite which amino acid sequence "comprising the amino acid sequence 56 to 70 of Smac" refers to. Office Action at 4. Applicants have canceled claim 27 and added new claims 45-52 which refer to the specific amino acid sequence by sequence identifier (*i.e.* SEQ ID NO:1 or SEQ ID NO:3). Thus, Applicants believe this objection to be moot.

The Examiner also objected to claim 30 for reciting "wherein the Smac protein is a fragment or derivative comprising amino acids 56 to 62 or 56 to 59 of Smac" when the claim already defined the Smac protein as the protein disclosed in GenBank accession no. AAF87716." Office Action at 4. Applicants have canceled claim 30 and added new claims 45-52, thus Applicants believe this objection to be moot.

The Examiner objected to claim 33 because a Markush-type claim should recite alternatives in a format such as "selected from the group consisting of". Office Action at 5. Applicants have canceled claim 33 and included Markush-type language in new claims 45-52. Thus, Applicants believe the objection to be moot.

The Examiner also objected to claim 33, requesting the term "and" be added before "amilomer" and to claims 25-30 because the term "aminoacid" should be spelled "amino acid". Office Action at 5. Applicants have canceled claims 25-30 and claim 33. New claims 45-52 recite the term "amino acid." Thus, Applicants believe the objection to be moot.

III. Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 23-34 and 44 under 35 U.S.C. § 112, second paragraph for allegedly being vague and indefinite for reciting GenBank accession numbers. Office Action at 5. Applicants respectfully traverse this ground for rejection. Applicants have canceled claims 23-34 and 44, but will respond to the Examiner's rejection as it may relate to new claims 45-52.

Applicants have amended the specification to include the sequences of the GenBank accession numbers referenced in the application and in the claims. Additionally, Applicants have added references to the sequence identifiers for the sequences of GenBank accession

numbers AAF87716 and CAA45921, SEQ ID NOs: 1 and 3 respectively, to new claims 45-52. As discussed *infra*, the addition of these sequences does not introduce new matter. Thus, Applicants respectfully request the Examiner reconsider and withdraw the present rejection.

IV. Rejection Under 35 U.S.C. § 112, First Paragraph (enablement)

The Examiner rejected claims 23-34 and 44 under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the enablement requirement. Office Action at 6. Applicants respectfully traverse this ground for rejection. Applicants have canceled claims 23-34 and 44, but will respond to the Examiner's rejection as it may relate to new claims 45-52.

Specifically, the Examiner maintains that the recitation of the GenBank accession numbers AAF87716 (Smac protein) and CAA45921 (HIV Tat protein) are not "sufficient so as to enable the skilled artisan to make and use the invention." *Id.* The Examiner has required amendment of the specification to include the sequence of the GenBank accession numbers. *Id.*

Applicants have added new claims which refer specifically to SEQ ID NO:1 (Smac protein) and SEQ ID NO:3 (TAT protein). Additionally, Applicants submit herewith a sequence listing including the sequences from GenBank accession numbers disclosed in the specification and priority documents EP 02008199.8 and EP 02015499.3. Specifically, Applicants have included the Smac polypeptide of GenBank accession no. AAF87716 (SEQ ID NO:1), the polynucleotide encoding the Smac polypeptide as disclosed in GenBank accession no. AF262240 (SEQ ID NO:2), the HIV-1 tat polypeptide of GenBank accession no. CAA45921 (SEQ ID NO:3) and the polynucleotide encoding the HIV-1 Genome of GenBank accession no. M15654 (SEQ ID NO:4).

The GenBank accession numbers referred to above may be found on page 4, line 15; page 6, lines 9-10; and page 16, line 1 of the International Publication No. WO 03/086470, which corresponds to the present application. Additionally, the GenBank accession numbers AAF87716, AF262240; and CAA45921 may be found in priority document EP 02015499.3 on page 2, line 28; page 6, lines 4-5 and page 12, lines 15-16. Finally, the GenBank accession

numbers AAF87716, AF262240; and M15654 may be found in priority document EP 02008199.8 on page 2, line 28; page 6, line 5 and page 15, line 4.

Applicants also submit herewith copies of each of the GenBank entries and their respective sequence revision histories as Exhibits 1-4. Genbank accession numbers AAF87716 and AF262240 have never been revised since their original GenBank submission. *See* Exhibits 1 and 2. GenBank accession numbers CAA45921 and M15654 have been revised, however the version numbers of the sequences have remained the same as indicated on the sequence revision history of each submission. *See* Exhibits 3 and 4. The revisions indicated in the histories for GenBank accession numbers CAA45921 and M15654 do not relate to revisions in the sequences. A revision of a sequence itself would have changed the version number of the sequence, according to the National Center for Biotechnology Information (NCBI). Thus, Applicants believe the sequences contained within the GenBank accession numbers referred to in the specification and priority documents and the sequences submitted herewith in the sequence listing to be the same sequences. As such, Applicants believe that the amendment to include the sequence listing filed herewith does not introduce new matter.

Additionally, Applicants file herewith a declaration stating that the sequence listing being added by way of amendment is the material previously incorporated by reference and thus the amendment does not contain new matter. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the rejection in light of the amendments to the specification and claims.

The Examiner also rejected claims 23-26, 31-34 and 44 under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the enablement requirement. Office Action at 14. Applicants respectfully traverse this ground for rejection. Applicants have canceled claims 23-26, 31-34 and 44, but will respond to the Examiner's rejection as it may relate to new claims 45-52.

Specifically the Examiner maintained that the specification while being enabling for a Smac protein/carrier entity comprising a full length Smac protein, or a Smac peptide

consisting of the amino acid fragment 56-70, 56-62, or 56-59 of the full length Smac protein, and a carrier comprising the full length TAT protein, or the protein transduction domain of TAT consisting of the amino acid fragment 37-72 or 47-57 of the full length TAT protein, does not reasonably provide enablement for a Smac protein/carrier entity...comprising any and all fragments or derivatives of the full length Smac protein, and a carrier that is any and all fragments or derivatives of the full length TAT protein." *Id.* Applicants respectfully disagree.

Solely in an effort to expedite prosecution, and not acquiescing in the propriety of the rejection, Applicants have added new claims 45-52 which recite the full length Smac protein (SEQ ID NO:1) and Smac fragments having the amino acid sequence of amino acids 56-70, 56-62 and 56-59 of SEQ ID NO:1. Additionally, new claims 45-52 recite the full-length TAT protein of SEQ ID NO:3 and TAT polypeptide fragments having the amino acid sequence of amino acids 37-72 and 47-57 of SEQ ID NO:3. Thus in view of the new claims, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

V. Rejections Under 35 U.S.C. § 112, first paragraph (written description)

The Examiner rejected claims 23-36, 31-34 and 44 under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement. Office Action at 8. Applicants have canceled claims 23-36, 31-34 and 44, but will respond to the Examiner's rejection as it may relate to new claims 45-52.

Specifically, the Examiner alleged that the written description of the specification is "not commensurate in scope with the claims which read on any and all fragments and derivatives of Smac and TAT protein." Office Action at 9. The Examiner further maintains that the specification does "not disclose any derivatives of Smac and TAT protein" and "only teaches fragments of Smac that are 56-70, 56-62 and 56-59 of Smac...and 37-72 and 47-57 of TAT protein...." *Id.* Applicants respectfully disagree.

Solely in an effort to expedite prosecution, and not acquiescing in the propriety of the rejection, Applicants have added new claims 45-52 which recite Smac fragments having the amino acid sequence of amino acids 56-70, 56-62 and 56-59 of SEQ ID NO:1. Additionally,

new claims 45-52 recite TAT fragments having the amino acid sequence of amino acids 37-72 and 47-57 of SEQ ID NO:3. Thus, Applicants respectfully request that the Examiner withdraw the rejection.

VI. Rejections Under 35 U.S.C. § 103(a)

The Examiner rejected claims 23-34 and 44 under 35 U.S.C. § 103(a) for allegedly being unpatentable over International Publication No. WO 02/16418 to Alnemri ("Alnemri") in view of International Publication No. WO 02/16402 to Wang ("Wang") and Ford *et al.*, *Gene Therapy* 8:1-4 (2001) ("Ford"). Office Action at 24. Applicants have canceled claims 23-34 and 44, but will respond to the Examiner's rejection as it may related to new claims 45-52.

Specifically, the Examiner alleges that Alnemri discloses a "mature Smac that is a Smac polypeptide without the 55 amino acid residue mitochondrial targeting sequence (MTS), [and that] the first 7 residues of mature Smac, Smac-N7, SEQ ID NO:6 and the first 35 residues of mature Smac, Smac-N35, SEQ ID NO:11...could be used as promoters of caspase enzymatic activity at attainable concentrations to kill cancer cells that overexpress IAPs." *Id.*

The Examiner also alleges that Wang discloses a composition comprising a peptide for inducing cancer cell apoptosis and an additional therapeutic agent wherein the peptide is amino acids 56-59, 56-60, 56-61 or 56-62 of the full length Smac protein. Office Action at 25. Finally, the Examiner alleges that Ford discloses that "TAT-mediated delivery can be improved by constructing fusion proteins between several polypeptides and proteins and the 47-57 region of the TAT protein." Office Action at 25.

Finally, the Examiner alleges that Ford discloses that "TAT-mediated delivery can be improved by constructing fusion proteins between several polypeptides and proteins and the 47-57 region of the TAT protein." *Id.* The Examiner thus concludes that it "would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to chemically link the Smac peptide or polypeptide of Alnemri or Wang to the 37-72 or 47-57 residue of TAT." Office Action at 26. The Examiner further argues that one would have

been motivated to link the proteins of Alnemri or Wang because Ford discloses that "proteins when linked to the 37-72 or 47-57 residue of TAT protein can be effectively delivered into cell cytoplasm or nucleus." *Id.*

Applicants respectfully disagree with the Examiner and maintain that Ford teaches away from the subject matter of the present invention. Specifically, one of skill in the art would not have considered using the TAT protein to deliver a protein to induce apoptosis in tumor cells. One of skill in the art would not have chosen TAT because of its ability to transactivate genes and induce proliferation of cancer cells, thus negating any apoptotic-inducing effects of the Smac protein and/or additional apoptotic inducing compounds.

Indeed, Ford discloses that the full-length TAT protein "stimulates growth of Kaposi's sarcoma-derived cells and that TAT transgenic mice develop Kaposi sarcoma." Ford at 2. Thus, one of skill in the art would not have been motivated to link the TAT protein to the Smac protein for inducing apoptosis as a cancer treatment, especially when the TAT protein was shown to stimulate certain types of cancer. Additionally, Ford discloses that "the transactivation potential of endogenous cellular genes by the 11 aa TAT PTD [amino acids 47-57 of TAT] is not known and will have to be monitored closely in the future" and that "if the 11 aa TAT PTD is shown to be devoid of toxic effects *in vivo*, it will be of tremendous use in future." Ford at 2-3.

Thus, a person of skill in the art would not have been motivated to use the TAT peptide of Ford for inducing apoptosis in tumor cells since the TAT protein itself has a contrary effect, *i.e.* induces the growth of tumor cells. Additionally, one of skill in the art would not have been motivated to use the 11 amino acid fragment of TAT since Ford comments that the toxic effects of the protein *in vivo* are not known. Additionally, the Examiner has failed to show any motivation for one of skill in the art to have selected TAT, or fragments of TAT, over the other disclosed transducing polypeptides of Ford such as Antennapedia or the herpes simplex virus VP22 protein. Thus, Applicants argue that it would not have been *prima facie* obvious to link Smac proteins to TAT for inducing apoptosis in a cancer cell and that Ford teaches away from such use. As such, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

VII. Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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